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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	28

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/984,900	D'APICE ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,46-51,67 and 70-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *67 and 70-73* is/are allowed.

6)☒ Claim(s) *1-3,46-51 and 74-81* is/are rejected.

7)☒ Claim(s) *80 and 81* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *26* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-17-01 has been entered.

Applicants' amendment filed 4-17-01 has been entered. Claims 1-3 and 46 have been amended. Claims 78-81 have been added. Claims 1-3, 46-51, 67 and 70-81 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 78 and 79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "conservative amino acid substitutions" in claim 1 is not described in the specification and is a new matter. The specification only discloses "minor amino acid variations" (page 6, lines 21-26) but fails to support the phrase "conservative amino acid substitutions".

The phrase "SSC at a concentration not greater than 0.5x" in claims 2 and 3 is not described in the specification and is a new matter. The specification only discloses "in 0.05x to 0.5x SSC" (page 7, line 13). The phrase "SSC at a concentration not greater than 0.5x" encompasses SSC concentration lower than 0.05x SSC. However, the specification fails to support SSC concentration lower than 0.05x SSC. Claims 78 and 79 depend on claims 2 and 3, respectively.

3. Claims 46-51, 74-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on any DNA construct comprising a disrupted porcine α-1-3 galactosyltransferase (GT) gene. The claims encompass any porcine α-1-3 GT gene derived from various species of pigs, or swines, which could have different nucleotide sequence of α-1-3 GT gene. The specification only discloses the nucleotide sequence of SEQ ID No. 7.

The claims read on a genus of disrupted α-1-3 GT genes and a genus of polynucleotide sequences that could be used for the disruption of the α-1-3 GT gene. The scope of the claim

includes numerous variants of SEQ ID No. 7 and polynucleotide sequence "comprising" a disrupted α-1-3 GT gene. The specification fails to provide description of the variations that could occur within SEQ ID No. 7 but still retain the porcine α-1-3 GT activity. Further, a DNA construct that "**comprises**" a disrupted porcine α-1-3 GT gene encompasses unknown and unidentified genomic sequences, such as the 5' and 3' flanking sequence to the various porcine α-1-3 GT genes and the nucleotide sequence that is irrelevant to porcine α-1-3 GT gene, that could be used for the disruption of a porcine α-1-3 GT gene. The genus of polynucleotide sequences that could be used for the disruption of the α-1-3 GT gene is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the polynucleotide class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the polynucleotide sequence SEQ ID No. 7 as disclosed in the present application is insufficient to describe the genus.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed DNA construct comprising a disrupted porcine α-1-3 GT gene. Thus it is concluded that the written description requirement is not satisfied for the genus of the polynucleotide sequences as claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID No. 7, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath*

makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 46-51 and 74-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al., 1992 (Brain Pathology, Vol. 2, p. 71-83) in view of Galili, 1993 (U2) and Hodges et al., 1996, US Patent No. 5,527,695 (B).

Claims 46-50 are drawn to a DNA construct comprising a disrupted porcine α-1,3 galactosyltransferase (α-1,3, GT) gene, wherein the disruption is accomplished by the insertion

of an exogenous sequence, such as a neo^R gene or a hyg^R gene, within regions such as exon 4, exon 7, exon 8, or exon 9 of the porcine α-1,3 GT gene. Claim 50 specifies the exogenous sequence is flanked at its 5' and 3' ends by FLP recombinase target site (FRT) DNA elements, and wherein stop codons have been inserted 3' to the selectable marker. Claims 51 and 74-77 are directed to a method for generating a porcine cell comprising at least one inactivated α-1,3 galactosyltransferase by introducing the DNA construct set forth above into porcine cells such that homologous recombination occurs between chromosome sequence and DNA construct.

Stanton teaches in vivo site-directed mutagenesis by homologous recombination to introduce a variety of mutations into mice. Stanton also teaches generating transgenic knockout mice via homologous recombination between the target vector containing selectable marker, such as neo, and target locus of embryonic cells (e.g. abstract, p. 75-77). Stanton does not teach inactivation of α-1,3 GT gene.

Galili discusses that the immunological barrier by anti-Gal interacting with α-galactosyl epitopes on the discordant graft cells might be difficult to overcome by means of immunosuppression, and suggests the use of xenografts devoid of α-galactosyl epitopes obtained from nonprimate donors which are genetically engineered to lack α-1,3 GT activity by gene knockout technology or by the production of transgenic animals with anti-sense DNA to the α-1,3 GT gene (e.g. p. 482).

Hodges teaches generating a DNA construct containing a FRT site and a selectable marker gene neo for a specific integration of a gene into the genome of an eukaryotic cell via homologous recombination (e.g. column 21, 22).

It would have been obvious for one or ordinary skill at the time of the invention to make a DNA construct comprising a disrupted α-1,3, GT gene because Stanton teaches using a target vector in introducing mutations to the targeted gene of a cell, and Galili teaches the presence of an α-1,3, GT gene and its role in xenotransplantation rejection. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a selectable marker gene such as neo and a FRT site for homologous recombination as taught by Hodges for generating a DNA construct comprising a disrupted porcine α-1,3, GT gene as taught by Galili and Stanton. It also would have been obvious to introduce an exogenous sequence within exon 4, 7, 8, or exon 9 of a porcine α-1,3,GT gene to interrupt α-1,3 GT gene because Stanton teaches introducing various mutations into a gene to alter the expression of said gene and the various locations of said exogenous gene are intended to interrupt α-1,3, GT gene and would be obvious for one of ordinary skill.

One having ordinary skill in the art would have been motivated to make a DNA construct comprising a disrupted α-1,3, GT gene and to have introduced said DNA construct into a porcine cell for generating a porcine cell with a specific disruption to an α-1,3, GT gene via homologous recombination of a FRT site and to select the transformed cells containing a disrupted α-1,3, GT gene with a selectable marker gene such as neo, because Galili suggests the use of xenografts

devoid of α-galactosyl epitopes obtained from nonprimate donors which are genetically engineered to lack α-1,3 GT activity by gene knockout technology and generation of a porcine cell comprising a disrupted α-1,3, GT gene would have allowed for the development of a porcine organ lacking α-1,3 GT activity . Such would have provided the benefit of preventing xenotransplant rejection in an animal patient.

Conclusion

6. Claims 1-3, 46-51 and 74-79 are rejected. Claims 80 and 81 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 67 and 70-73 are in condition of allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

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